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(54) Title of Invention:

A method for making a medicine which is hard to dissolve amorphous (non-crystalline)

(57) Abstract:

A method for manufacturing a solid dispersoid of a medicine which is hard to dissolve which is characterized by the heating the hardly soluble medicine, an amorphism (non-crystallization) inducing agent and an amorphism (non-crystallization) stabilizer or the mechanochemical treatment of the same; and a method for manufacturing a solid dispersoid of a medicine which is hard to dissolve which is characterized by the high-frequency heating of the medicine which is hard to dissolve and an amorphism stabilizer. These processes make it possible to make medicines which are hard to dissolve amorphous at a temperature lower than those employed in the conventional methods. The solid dispersoids of the amorphous medicines which are hard to dissolve obtained by these methods have an improved absorption rate from the mucous membranes and the rectum, which makes it possible to raise their bioavailability.

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Specification

A method for making a medicine which is hard to dissolve amorphous (non-crystalline)

Technical Field

The invention in question concerns a method for manufacturing a solid dispersoid by relying on a technique in which a medicine which is hard to dissolve is used effectively, and in particular a method for making such a medicine amorphous. This technique will be used in fields in which the quality of the elution of medicine is a problem, for example, in the fields of agricultural chemicals and medicines, perfumes and cosmetics, and the medical treatment, and in particular in the field of medical treatment.

Background Technique

In the design of formulations for internal use, the raising of bioavailability by improving the solubility and the absorbability of medicines which are difficult to dissolve is important from the standpoint of the effectiveness and safety of the said medicines.

As means for increasing the bioavailability of a medicine which is difficult to dissolve, there are methods from improving the solubility of the medicine by such things as the atomization and wetting of the medicine's particles and an improvement of its solubility, the creation of a solid dispersoid, the use of polymorphs, etc., but the use of polymorphs, etc., but the method which has the focus of attention in particular is the method whereby a solid dispersoid is manufactured by a method in which the medicine is made amorphous. The term a "solid dispersoid" stands for a dispersoid which has been kept in a state in which the medicine has been made completely amorphous, being something in which the medicine has been dispersed in a carrier in a monomolecular state. In general the non-crystalline form is in a high energy state compared to the crystal form, and is something for which a high degree of solubility can be anticipated.

The methods for manufacturing a solid dispersoid are broadly classified as the solvent method, the fusion method (the heating method), the fusion-solvent method, the mechanochemical method, and other.

The solvent method is a method whereby a solid dispersoid is obtained by the elimination/gas diffusion of the solvent in the presence of nuclear particles or in that state after both the medicine and the water soluble macromolecular base, which is a non-crystalline stabilization agent, have been dissolved in an organic solvent. This method suffers from the deficiencies that the costs of manufacture are high, and in addition that cases in which residual solvent for the medicine are concern can be observed given the fact that a large quantity of organic solvent is used, even though it is a method which is superior as a method for improving the solubility of a medicine which is hard to dissolve.

As for the fusion method (the heating method), this is a method involving the lowering of the melting point of a mixture of the medicine and the water soluble macromolecular base, which is the non-crystalline stabilization agent, the heating and kneading of the mixture at a temperature below the melting point of both its components, the dispersion of the medicine in a molecular state, and its cooling, caking and pulverization.

The fusion method is superior insofar as it does not involve the use of organic solvents. However, depending on the type of the medicine which is hard to dissolve, there are times when it is not possible to achieve the creation of an adequate amorphous (non-crystalline) state by only adding a non-crystallizing stabilizer as the carrier used for the fixed [Translator: There may be mistake here, and this might possibly read "solid", since one character appears to be wrong.] dispersoid.

In addition, in order to transform the medicine completely into an amorphous (non-crystalline) state, the process is conducted below the melting points of the medicine and the carrier used for the fixed [Translator: Same as in the preceding paragraph.] dispersoid, but it is necessary to carry out the kneading treatment at a high temperature, so one finds not only cases in which the medicine is degraded, the carrier deteriorates, etc., but also instances arise in which the non-crystallization process is insufficient.

For example, in the method in which only the medicine which is hard to dissolve and the water soluble macromolecular base, which is the amorphous stabilization agent, are employed, and heating and fusion of the two is conducted by employing a lowering of their melting points, the lowering of the melting point is at best 10 degrees Centigrade, perhaps solely so since the temperature of the thermal treatment becomes a high, or since it is common for the macromolecular base to be amorphous from the start, the apparent melt viscosity is high and the microdispersibility of the medicine and the water soluble macromolecules is poor, so there are times when it is not possible to achieve adequate non-crystallization depending on the medicine involved.

In addition, there have also been attempts at heating and fusion with medicines which are hard to dissolve by using as the carrier used for solid dispersoids not a water soluble macromolecular base but rather low molecular chemical compounds such as phosphatidylcholine, etc., as non-crystallization inducers. However, there are concerns that decomposition and reformation of the medicine will occur as a result of the heating treatment. Moreover, in the event that the temperature of the products treated by heating is lowered to room temperature, it proves difficult to maintain the amorphous state which has been achieved so there are concerns that the stability will be poor.

The mechanochemical method is a method in which a solid dispersoid is obtained by improving the promotion of the non-crystallization of the medicine solid and the promotion of the dispersion of the medicine which has been made amorphous (non-crystalline) to the carrier by employing mechanical energy such as compression, shearing, friction, etc. Concretely, there are such treatments as ball mill mixed grinding, planetary mill treatment, compression press treatment, shear roll mixed treatment, etc.

With the mechanochemical method, there are cases in which special machinery is necessary since (perhaps because the level of the mechanical energy is low) it is difficult to transform the medicine into an amorphous state solely by this means even in the event that an amorphous stabilization agent is added to the medicine which is hard to dissolve (Patent Disclosure Bulletin 4-818106).

As can be seen from the above, methods have been sought whereby it possible to obtain in an industrially inexpensive manner a solid dispersoid in a completely amorphous state at a price which is more inexpensive than previous methods.

Disclosure of the Invention

As a result of diligent examination in order to surmount the problems which remain in these prior methods, the inventors discovered a method for making a medicine which is hard to dissolve amorphous which is characterized by the fact that 3 components, namely (1) the medicine which is hard to dissolve; (2) an amorphism inducing agent; and (3) an amorphism stabilization agent are mixed together, and heating or mechanochemical treatment is then carried out on the mixture. In addition, they further discovered that high frequency heating is preferable to ordinary heater heating and steam heating as a heating treatment.

In addition, they discovered a method for making a medicine which is hard to dissolve amorphous which is characterized by the fact that components, namely (1) the medicine which is hard to dissolve; and (3) an amorphism stabilization agent are mixed together, and high frequency heating treatment is then carried out on the mixture.

Furthermore, it is also possible to manufacture a formulation of the medicine which is hard to dissolve which has employed the solid dispersoid obtained by means of the non-crystallization method which constitutes the invention in question.

The (1) medicine which is hard to dissolve in the invention in question is a medicine whose solubility in water is extremely low and whose absorption from the intestinal tract, the mucous membrane of the nose, the rectum, etc. is poor, a medicine for which an improvement of the absorption is difficult by the making of ordinary formulations, and a medicine for which the absorption can be raised by means of non-crystallization. For example, one can mention such examples as the chemical compounds of the dihydropyridine family such as nifedipine, nicardipine hydrochloride, phenacetin, digitoxin, diazepam, phenytoin, tolbutamide, theophylline, griseofulvin, chloramphenicol, etc.

As for the (2) amorphism inducing agent in the invention in question, it is acceptable if it is a chemical compound whereby the mixture between it and the medicine causes a lowering of the latter's melting point, and a crystalline chemical compound is particular desirable. This is a chemical compound which causes a transformation of the crystal lattice energy of the medicine which is hard to dissolve in a low energy direction, and moreover which possesses the function and property of increasing the fluctuations of the crystal lattice as the same temperature. The amorphism inducing agent which is selected differs in accordance with the kind of medicine which is hard to dissolve; for

example, in the event that an (a) basic medicine which is hard to dissolve is selected, then the selection of a neutral substance or an acidic substance, and an acidic substance in particular, is desirable, and in the event a (b) acidic medicine which is hard to dissolve is selected, then the selection of a neutral substance or an basic substance, and an basic substance in particular, is desirable.

Concretely, one can mention the following as examples of amorphism inducing agents: amino acids or their salts (aspartic acid and its Na salt, Mg salt, etc., glycine, alanine, glutamic acids and glutamic acid hydrochloride, etc.), asparatame, erythorbic acid and its salts (Na salt, etc.), ascorbic acid and its salts (Na salt, etc.), stearic acid ester, aminoethyl sulfonic acid, inositol, ethylurea, citric acid and its salts (salts like 3-Na, 2-Na, dihydrogen Na, Ca salt, etc.), glycyrrhetic acid and its salts (Na salts like 3-Na, 2-Na, etc., ammonium salts like diammonium, monoammonium, etc., K salt), gluconic acid and its salts (Na salt, Ca salt, Mg salt, etc.), creatinine, salicylic acid and its salts (Na salts, etc.), tartaric acid and its salts (Na salt, K-Na salt, hydrogen-K salt, etc.), succinic acid and its salts (Na salts such as 2-Na, 1-Na, etc.), calcium acetate, saccharin sodium, aluminum hydroxide, sorbic acid and its salts (K salts, etc.), dehydroacetic acid and its salts (Na salt, etc.), thiomalic acid sodium [sic], nicotinic acid amide, urea, fumaric acid and its salts (Na salt, etc.), the Macrogol group, maltose, maltol, maleic acid, mannitol, meglumine, desoxycholic acid sodium, phosphatidyl choline, etc.

Preferably, one can mention as the following as examples of the amorphism inducing agent: amino acids or their salts (aspartic acid and its Na salt, Mg salt, etc., glycine, alanine, glutamic acids and glutamic acid hydrochloride, etc.), ascorbic acid and its salts (Na salt, etc.), stearic acid ester, aminoethyl sulfonic acid, ethylurea, citric acid and its salts (salts like 3-Na, 2-Na, dihydrogen Na, Ca salt, etc.), glycyrrhetic acid and its salts (Na salts like 3-Na, 2-Na, etc., ammonium salts like diammonium, monoammonium, etc., K salt), creatinine, tartaric acid and its salts (Na salt, K-Na salt, hydrogen-K salt, etc.), succinic acid and its salts (Na salts such as 2-Na, 1-Na, etc.), urea, fumaric acid and its salts (Na salt, etc.), the Macrogol group, maltose, maltol, mannitol, meglumine, etc.

More preferably, one can mention as the following as examples of the amorphism inducing agent: amino acids or their salts (aspartic acid and its Na salt, Mg salt, etc., glycine, alanine, glutamic acids and glutamic acid hydrochloride, etc.), ethylurea, glycyrrhetic acid and its salts (Na salts like 3-Na, 2-Na, etc., ammonium salts like diammonium, monoammonium, etc., K salt), tartaric acid and its salts (Na salt, K-Na salt, hydrogen-K salt, etc.), succinic acid and its salts (Na salts such as 2-Na, 1-Na, etc.), urea, the Macrogol group, maltose, maltol, mannitol, meglumine, etc.

Still more preferably, one can mention as the following as examples of the amorphism inducing agent: glycyrrhetic acid and its salts (Na salts like 3-Na, 2-Na, etc., ammonium salts like diammonium, monoammonium, etc., K salt), succinic acid and its salts (Na salts such as 2-Na, 1-Na, etc.), urea, maltol, mannitol, etc.

In addition, the lowering of the melting point of the amorphism inducing and the medicine which is hard to dissolve differs depending on the combination with the medicine which is hard to dissolve, but one can preferably use a chemical compound

which lowers the melting point by 5 degrees Centigrade or more than the melting point of the medicine which is hard to dissolve.

Still more preferably, one can use a chemical compound which lowers the melting point of the mixture of amorphism inducing agent and the medicine which is hard to dissolve by 15 degrees Centigrade or more than the melting point of the medicine which is hard to dissolve, and most preferably of all one can use a chemical compound which lowers the former melting point by 25 degrees Centigrade or more than the latter.

In the event that the heating used is high frequency heating, it is possible to make the medicine which is hard to dissolve amorphous by high frequency heating of a mixture of only the medicine which is hard to dissolve and an amorphism stabilizer without employing an amorphism inducing agent. Naturally, high frequency of 3 components in which an amorphism inducing agent has been mixed also provides a full effect.

After the crystal structure of the medicine which is hard to dissolve has been caused to fluctuate by the amorphism inducing agent, the amorphism stabilizer stabilizes the amorphous state by the interaction of its crystal lattice on the fluctuating state.

Therefore, if it is an amorphism stabilizer which possesses the above-mentioned activity it is possible to use this stabilizer in the invention in question. In other words, it is acceptable to use anything for an amorphism stabilizer provided that it is a chemical compound that preserves the functional group which possesses an interaction with the medicine which is hard to dissolve, but it is preferable to use a chemical compound whose solubility with the medicine which is hard to dissolve is great, which possesses a flexible functional group, and which has a high degree of thermal stability, for example, the amorphous macromolecular bases listed below. The phrase "a chemical compound whose solubility with the medicine which is hard to dissolve is great" refers to a chemical compound for which the values of the solubility parameters (Solubility Parameter: Encyclopedia of Polymer Science and Engineering, volume 15, page 393, John Wiley and Sons, Inc., 1989) are close. Still more preferable is a chemical compound in which the amorphism stabilizer has a solubility which is highly compatible with not the medicine which is hard to dissolve but also the amorphism inducing agent.

In addition, the functional group of the interacting amorphism stabilizer which is selected differs in accordance with the type of medicine which is hard to dissolve, so in the event that an (a) basic medicine which is hard to dissolve is selected, then the selection of a neutral substance or an acidic substance, and an acidic substance in particular, is desirable, and in the event a (b) acidic medicine which is hard to dissolve is selected, then the selection of a neutral substance or a basic substance, and a basic substance in particular, is desirable.

In the invention in question, one can mention the following as examples of the (3) amorphism stabilizer: cellulose inducers (for example, hydroxyethylcellulose, hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose - acetate succinate (HPMC - AS), methylcellulose, ethylcellulose, carboxymethylcellulose, cellulose acetate phthalate, etc.), polyvinylpyrrolidone, crosslinked polyvinylpyrrolidone,

polyvinyl alcohol, polyvinyl acetate, vinyl alcohol – vinyl acetate copolymer, ethylene – vinyl acetate copolymer, polyethylene oxide inducers (for example, polyethylene glycol, polyoxyethylene polyoxypropylene cetyl ether, polyoxyethylene alkyl ether, polyoxyethylene oxyphenyl ether, polyoxyethylene oleyl amine, polyoxyethylene oleyl ether, polyoxyethylene oleyl ether sodium phosphate, polyoxyethylene hardened castor oil, polyoxyethylene stearyl ether, polyoxyethylene stearyl ether phosphate, polyoxyethylene cetyl ether, polyoxyethylene cetyl ether sodium phosphate, polyoxyethylene sorbit beeswax, polyoxyethylene nonylphenyl ether, polyoxyethylene castor oil, polyoxyethylene behenyl ether, polyoxyethylene polyoxypropylene glycol, polyoxyethylene polyoxypropylene cetyl ether, polyoxyethylene lauryl ether, polyoxyethylene lanolin, polysorbate 40, polysorbate 60, polysorbate 65, polysorbate 80, etc.), polystyrene sodium sulfonate, gelatin, soluble starch, Pullulan, dextran, gum arabic, chondroitin sulfate and its Na salts, hyaluronic acid, pectin, chitin, chitosan, alpha-, beta-, or gamma – cyclodextrine, alginic acid inducers (for example, methacrylic acid inducers like alginic acid and its Na salts and propylene glycol ether, etc.), the acrylic resin family (methacrylic acid, methyl methacrylate, butyl methacrylate, dimethylaminoethyl methacrylate, trimethyl ammonium ethyl chloride methacrylate, acrylic acid, ethyl acrylate, etc.. and/or the homopolymers and copolymers of acrylic acid inducers such as amino alkyl – methacrylate copolymer, methyl methacrylate – methacrylic acid copolymer, methacrylic acid – ethyl acrylate copolymer, methacrylic acid – n-butyl acrylate copolymer, acrylic ester – vinyl acetate copolymer, 2-ethylhexyl acrylate – vinyl pyrrolidone copolymer, starch acrylate, etc.), and polyvinyl acetol diethylaminoacetate, etc.

In addition, it is also possible to use chemical compounds possessing a gel formation capability, such as silicon dioxide, aluminium hydroxide, etc., as the amorphism stabilizer of the invention in question.

Preferably, one can mention as the following as examples of the amorphism stabilizer: hydroxyethylcellulose, hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose – acetate succinate (HPMC – AS), polyvinylpyrrolidone, polystyrene sodium sulfonate, alpha-, beta-, or gamma – cyclodextrine, the acrylic resin family (methacrylic acid, methyl methacrylate, butyl methacrylate, dimethylaminoethyl methacrylate, trimethyl ammonium ethyl chloride methacrylate, acrylic acid, ethyl acrylate, etc.. and/or the homopolymers and copolymers of acrylic acid inducers, etc.), and polyvinyl acetol diethylaminoacetate, etc.

More preferably, one can mention as the following as examples of the amorphism stabilizer: hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose – acetate succinate (HPMC – AS), polyvinylpyrrolidone, the acrylic resin family (methacrylic acid, methyl methacrylate, butyl methacrylate, dimethylaminoethyl methacrylate, trimethyl ammonium ethyl chloride methacrylate, acrylic acid, ethyl acrylate, etc. and/or the homopolymers and copolymers of acrylic acid inducers, etc.), and polyvinyl acetol diethylaminoacetate, etc.

The types and ratios of the combination of the (1) the medicine which is hard to dissolve; (2) an amorphism inducing agent; and (3) an amorphism stabilizer are selected appropriately in accordance with the type of medicine which is hard to dissolve, but the

usual ratio by weight is as follows: (1) : (2) : (3) = 1 : (0.1 – 10) : (0.1 – 10), with a ratio of (1) : (2) : (3) = 1 : (0.3 – 3) : (0.3 – 8) being preferable, and a ratio of (1) : (2) : (3) = 1 : (0.3 – 2) : (0.5 – 5) being still more preferable.

As for the solid dispersoid of the medicine which is hard to dissolve, first the three necessary components, (1) the medicine which is hard to dissolve; (2) an amorphism inducing agent; and (3) an amorphism stabilizer, are granulated (mixed) in a wet or dry manner, and at the same time as or after the mixing of this mixture the solid dispersoid is obtained by either thermal treatment at a temperature higher than that at which the induction of amorphism starts and moreover at a temperature at which the medicine which is hard to dissolve will not be degraded and deteriorate, or mechanochemical treatment under the same energy conditions as this heating treatment. It is preferable that the heating temperature of the mixture at this time be set at a level below the melting point of the medicine which is hard to dissolve, and also preferable that the temperature be as close as possible to the temperature at which the induction of amorphism starts. If the heating temperature is lower than the temperature at which the induction of amorphism starts by for example 5 to 10 degrees Centigrade, the non-crystallization process will not proceed fully.

The meaning of the phrase “a temperature at which the induction of amorphism starts” refers to the temperature at the start of endothermy (the temperature of the start of the peak) which is observed when one measures a rise in temperature of 10 degrees Centigrade per minute using a Differential Scanning Calorimeter (DSC) for 10 mg of the mixture sample (1 : 1) of the medicine which is hard to dissolve and the amorphism inducing agent..

As for the methods for granulation, there is no need for a special method; rather, a universal mixing machine, a flow granulation device, a dash mill, a wet granulation machine, a dry granulation machine, etc., are used. Moreover, it is acceptable to carry out thermal treatment at the time of granulation, and after granulation it is acceptable to conduct non-crystallization by carrying out heating treatment with, for example, a plate-style drying machine, a fluidized drying machine, a gyro drying machine, a powder drying machine, etc., by such heating methods as heating by an ordinary heater, steam heating, infrared heating, far infrared heating, etc.

Moreover, it is possible to carry out non-crystallization by employing not only heat but also mechanochemical treatment based on such forms of mechanical energy as compression, shearing, friction, etc. For example, it is possible to carry out non-crystallization by employing only mechanochemical treatment by such treatments as ball mill powderizing, planetary mill treatment, compression press treatment, shearing roll treatment, a kneader, etc. without any heating of the above-mentioned 3 components. By relying on these methods, it is possible to carry out non-crystallization for medicines which are unstable in relation to heat.

In addition, it is also possible to employ the vibrating energy of ultrasonic waves, etc., and electromagnetic energy treatments such as electrical fields, magnetism, etc., as the energy for creating a state of flux in the crystal lattice in the medicine which is hard to dissolve among the 3 components of the mixture.

Either thermal treatment at the temperature of amorphism induction or mechanical energy treatment under the same conditions is acceptable. As far as the treatment time for non-crystallization is concerned, it is preferable from the standpoint of quality control, uniformity, and energy conservation that this usually be between 20 and 120 minutes, and preferably between 30 and 90 minutes, in the case of thermal treatment, and usually between 1 and 20 minutes, and preferably between 3 and 10 minutes, in the case of mechanical energy treatment.

In the event of heating treatment, it is also possible to use high frequency wave heating treatment in addition to the above-mentioned usual heating treatments.

It is possible to select the frequency band to be used in accordance with the bodies to be heated, and microwave heating employing the microwave band is particularly desirable. It is possible to use as the frequencies for microwave heating the 4 frequencies allotted as ISM (Industrial, Scientific, and Medical) frequencies by the Wireless Telegraphy Act, namely 915, 2450, 5800, and 22125 MHz. In general the 915 and 2450 frequencies are used.

As far as the method of the microwave heating is concerned, it is possible to select either the oven style (microwave oven, conveyor style) or the wave guide style depending on the shape of the item to be heated.

In the event of high frequency wave heating, the amorphism induction agent is not a necessary component, and the types and ratios of the combination of the (1) the medicine which is hard to dissolve (3) an amorphism stabilizer are selected appropriately in accordance with the type of medicine which is hard to dissolve, but the usual ratio by weight is as follows: (1) : (3) = 1 : (0.1 – 10), with a ratio of (1) : (3) = 1 : (0.3 – 8) being preferable, and a ratio of (1) : (3) = 1 : (0.5 – 5) being still more preferable.

In this case, the solid dispersoid of the medicine which is hard to dissolve is obtained by first granulating (mixing) (1) the medicine which is hard to dissolve and (3) an amorphism stabilizer in a wet or dry manner, and at the same time as or after the mixing of this mixture high frequency wave heating is carried out.

The treatment time required for non-crystallization by high frequency wave heating depends on the output of the high frequency waves, but it is preferable from the standpoint of quality control, uniformity, etc. that this usually be between 3 and 40 minutes, and preferably between 5 and 30 minutes, in the case of batch treatment. In the case of continuous conveyor-style treatment, it is possible to determine the treatment time by calculating based on the energy required for non-crystallization in the batch treatment. With high frequency wave heating one can obtain a solid dispersoid with a high degree of uniformity in a short time compared to the time required by ordinary thermal treatments.

As for the methods for granulation (mixing), there is no need for a special method; rather, a universal mixing machine, a flow granulation device, a dash mill, a wet granulation machine, a dry granulation machine, etc., are used. Moreover, it is acceptable to carry out ordinary thermal treatment or the mechanochemical treatments described

above (for example, ball mill powderizing, planetary mill treatment, compression press treatment, shearing roll treatment, a flow coater, a kneader, etc.) at the time of granulation, and after granulation it is acceptable to conduct out ordinary thermal treatment or the mechanochemical treatments described above by carrying out heating treatment with, for example, a plate-style drying machine, a fluidized drying machine, a gyro drying machine, a powder drying machine, etc.

In addition, it is possible to conduct thermal treatment, high frequency wave heating, and mechanochemical treatment in combination.

It is also possible to carry out non-crystallization by combining water, a surface activation agent, an anti-oxidation agent, preservatives, a stabilizer, etc., in addition to the 3 necessary components, (1) the medicine which is hard to dissolve, (2) the amorphism inducing agent, and (3) the amorphism stabilizer, in the non-crystallization of the medicine which is hard to dissolve which constitutes the invention in question. In addition it is possible to carry out crystallization by combining one component or 2 or more components for (2) the amorphism inducing agent and (3) the amorphism stabilizer, respectively.

In the method for manufacturing the solid dispersoid of a medicine which is hard to dissolve which is obtained by means of the non-crystallization method which constitutes the invention in question and the orally administered preparation which contains the solid dispersoid, it is possible to add as appropriate an excipient (for example, crystal cellulose, milk sugar, etc.), a disintegrating agent, a lubricant, a coloring agent, etc. in addition to the above-mentioned necessary components.

Optimal Form for the Implementation of the Invention

An explanation employing working examples follows below concerning the necessity of the 3 necessary components, (1) the medicine which is hard to dissolve, (2) the amorphism inducing agent, and (3) the amorphism stabilizer, and their heating or mechanochemical treatment, of the invention in question, and moreover of the necessity of the high frequency wave heating of (1) the medicine which is hard to dissolve and (3) the amorphism stabilizer.

Experimental Methods 1

10 mg of the test substance is measured with a Differential Scanning Calorimeter (DSC) at a speed of temperature increase of 10 degrees Centigrade per minute. The peak temperature of the endothermic peak is taken to be the melting point of the test substance. Taking a combination of the medicine which is hard to dissolve and the amorphism inducing agent (1 : 1) as the test material, the temperature at the start of endothermy (the temperature of the start of the peak) which is observed when one measures using a DSC is taken to be the temperature at which amorphism is induced.

Experimental Methods 2

The degree of crystallization is measured by X-ray powder diffraction measurement. Readings are taken of the strength of diffraction (S0) in the diffraction angle 2θ which originates in the medicine which is hard to dissolve after the conducting of X-ray powder diffraction measurements for a simple mixed text substance containing the 3 components, the medicine which is hard to dissolve, the amorphism inducing agent, and the amorphism stabilizer. Similarly, readings are taken of the strength of diffraction (S2) of the medicine which is hard to dissolve with the test material on which heating treatment has been carried out, and a plot is made for each crystal peak with S0 corresponding to the horizontal axis and S1 corresponding to the vertical axis. Approximating by the regression line which passes the point of origin, its slope is multiplied by a factor of 100 and taken to be the degree of crystallization (%). For example, in the event that the degree of crystallization does not change, in other words, in the event that it is 100%, the angle of elevation of the regression line is 45 degrees, so the slope is 1. In the event that the degree of crystallation is 10%, the slope is 0.1.

Working Example 1

5g of water were added to a mixture of 10g of nifedipine, 10g of succinic acid, and 20g of HPMC – AS and wet granulation was conducted, and a solid dispersoid was obtained after heating at 160 degrees Centigrade for 1 hour. The crystalline peak of the nifedipine could not be recognized for this solid dispersoid. This was granulated by the usual method. As far as the melting points are concerned, that of nifedipine is 175 degrees Centigrade, that of succinic acid is 192 degrees Centigrade, and that of the mixture of nifedipine and succinic acid was 167 degrees Centigrade, and the temperature at which amorphism started was 158 degrees Centigrade.

Working Example 2

A mixture of 150g of nicardipine chloride, 100g of urea, and 150g of hydroxypropylmethylcellulose (HMPC [sic]) was thermally treated for one hour at 115 degrees Centigrade with a plate-style drying machine under ordinary pressure and a solid dispersoid was obtained. No crystalline peak of the nicardipine chloride could be recognized for this solid dispersoid.

As far as the melting points are concerned, that of nicardipine chloride is 170 degrees Centigrade, that of urea is 137 degrees Centigrade, and that of the mixture of nicardipine chloride and urea was 129 degrees Centigrade, and the temperature at which amorphism started was 115 degrees Centigrade.

100g of crystal cellulose and 10g of milk sugar were added to 300g of this solid dispersoid and after dry granulation by the usual method solid tablets were obtained by tablet making.

Working Example 3

Using a high speed planetary mill, a mixture of 3g of nicardipine chloride, 1g of urea, and 5g of HPMC was treated for 3 minutes at 100G. The results of the X-ray powder diffraction measurements were that no crystalline peak could be recognized.

Working Example 4

Instead of the heating treatment of 1 hour at 160 degrees Centigrade as in Working Example 1, heating was carried out by microwaves (700W) for 20 minutes using a microwave drying machine (frequency 2450 MHz), and a solid dispersoid was obtained. No crystalline peak of the nifedipine could be recognized for this solid dispersoid, and it was amorphous.

Working Example 5

20g of water was added to 20g of nicardipine chloride and 40g of hydroxypropylmethylcellulose – acetate succinate (HPMC – AS), wet granulation was conducted, and heating was conducted with microwaves (700W) for 15 minutes using a microwave drying machine (frequency 2450 MHz), and a solid dispersoid was obtained thereby. No crystalline peak of the nicardipine chloride could be recognized for this solid dispersoid.

50g of crystal cellulose and 50g of milk sugar were added to 50g of this solid dispersoid, and after dry granulation by the usual method solid tablets were obtained by tablet making.

Working Example 6

5g of water was added to 3g of tolbutamide and 6g of hydroxypropylmethylcellulose – acetate succinate (HPMC – AS), the combination was mixed in a mortar, and heating was conducted with microwaves (500W) for 20 minutes using a microwave drying machine (frequency 2450 MHz), and a solid dispersoid was obtained thereby. No crystalline peak of the tolbutamide could be recognized for this solid dispersoid.

Working Example 7

5g of theophylline, 2g of succinic acid and 15g of polyvinyl pyrrolidone were dry granulated [**Translator: One wrong character in the text.**] and heating was conducted with microwaves (500W) for 20 minutes using a microwave drying machine (frequency 2450 MHz), and a solid dispersoid was obtained thereby. No crystalline peak of the theophylline could be recognized for this solid dispersoid.

Comparative Example 1

Working example 1 was carried out in exactly the same manner except that only one of the following changes was introduced.

1 – A: Only the succinic acid (the amorphism inducing agent) was omitted.

1 – B: Only the HPMC - AS (the amorphism stabilizer) was omitted.

1 – C: Thermal treatment was conducted at 140 degrees Centrigade (a temperature which is lower than 158 degrees Centigrade, which is the temperature at which the induction of amorphism starts).

There was absolutely no amorphism in any of these cases, and the product was not a complete solid dispersoid.

Degree of crystallization of the nifedipine

Working Example 1: No crystalline peak could be recognized.

1 – A: 50%

1 – B: An X-ray powder diffraction peak which is different from that of nifedipine was recognized.

1 – C: 100%

Comparative Example 2

Working example 2 was carried out in exactly the same manner except that only one of the following changes was introduced.

2 – A: Only the-urea (the amorphism inducing agent) was omitted.

2 – B: Only the HPMC (the amorphism stabilizer) was omitted.

2 – C: Thermal treatment was conducted at 100 degrees Centrigade (a temperature which is lower than 115 degrees Centigrade, which is the temperature at which the induction of amorphism starts).

There was absolutely no amorphism in any of these cases, and the product was not a completely solid dispersoid.

Degree of crystallization of the nicardipine chloride

Working Example 2: No crystalline peak could be recognized.

2 – A: 85%

2 – B: An X-ray powder diffraction peak which is different from that of nicardipine chloride was recognized.

2 – C: 95%

Comparative Example 3

In Working Example 3, an experiment was conducted in which only the urea (the amorphism inducing agent) was omitted, and the results of the X-ray powder diffraction was that the degree of crystallization was 80%.

Comparative Example 4

Other than the fact that heating treatment was carried out for 1 hour at 115 degrees Centigrade by a plate-style drying machine in the place of the microwave heating in Working Example 5, everything was carried out in exactly the same manner as in Working Example 2.

The degree of crystallization of the nicardipine chloride was 70%, and the product was not a completely solid dispersoid.

Scope of Claims

1. The method for manufacturing a solid dispersoid of a medicine which is hard to dissolve which is characterized by the heating or mechanochemical treatment of the medicine which is hard to dissolve, an amorphism inducing agent, and an amorphism stabilizer.

2. The manufacturing method recorded in Claim 1 in which the heating is high frequency wave heating.

3. The method for manufacturing a solid dispersoid of a medicine which is hard to dissolve which is characterized by the high frequency wave heating of the medicine which is hard to dissolve and an amorphism stabilizer.

4. The manufacturing method recorded in Claim 1 in which the following are examples of amorphism inducing agents: amino acids or their salts, aspartame, erythorbic acid and its salts, ascorbic acid and its salts, stearic acid ester, aminoethyl sulfonic acid, inositol, ethylurea, citric acid and its salts, glycyrrhetic acid and its salts, gluconic acid and its salts, creatinine, salicylic acid and its salts, tartaric acid and its salts, succinic acid and its salts, calcium acetate, saccharin sodium, aluminum hydroxide, sorbic acid and its salts, dehydroacetic acid and its salts, thiomalic acid sodium [sic], nicotinic acid amide, urea, fumaric acid and its salts, the Macrogol group, maltose, maltol, maleic acid, mannitol, meglumine, desoxylcholic acid sodium, phosphatidyl choline, etc.

5. The manufacturing method recorded in Claim 1 in which the following are examples of amorphism stabilizers: cellulose inducers, polyvinylpyrrolidone, crosslinked polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, vinyl alcohol – vinyl acetate copolymer, ethylene – vinyl acetate copolymer, polyethylene oxide inducers, polystyrene

sodium sulfonate, gelatin, soluble starch, Pullulan, dextran, gum arabic, chondroitin sulfate and its Na salts, hyaluronic acid, pectin, chitin, chitosan, alpha-, beta-, or gamma - cyclodextrine, alginic acid inducers, the acrylic resin family, polyvinyl acetol diethylaminoacetate, silicon dioxide, aluminium hydroxide, etc.

6. The manufacturing method recorded in Claim 3 in which the following are examples of amorphism stabilizers: cellulose inducers, polyvinylpyrrolidone, crosslinked polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, vinyl alcohol - vinyl acetate copolymer, ethylene - vinyl acetate copolymer, polyethylene oxide inducers, polystyrene sodium sulfonate, gelatin, soluble starch, Pullulan, dextran, gum arabic, chondroitin sulfate and its Na salts, hyaluronic acid, pectin, chitin, chitosan, alpha-, beta-, or gamma - cyclodextrine, alginic acid inducers, the acrylic resin family, polyvinyl acetol diethylaminoacetate, silicon dioxide, aluminium hydroxide, etc.

7. The preparation which is characterized by the fact that it contains a solid dispersoid of the medicine which is hard to dissolve which is obtained by means of the methods of manufacture recorded in any one of the claims from Claim 1 to Claim 6 above.